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Clinical science

Prevalence and identification of neuropsychiatric symptoms in systemic autoimmune rheumatic diseases: an international mixed methods study

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Abstract

Objective: A limited range of neuropsychiatric symptoms have been reported in systemic autoimmune rheumatic diseases (SARDs), with varied symptom prevalence. This study aimed to investigate a wider range of potential symptoms than previous studies, compare patient self-reports with clinician estimates, and explore barriers to symptom identification.

Methods: Mixed methods were used. Data from SARDs patients ($n = 1853$) were compared with controls ($n = 463$) and clinicians ($n = 289$). In-depth interviews ($n = 113$) were analysed thematically. Statistical tests compared means of survey items between patients and controls, 8 different SARD groups, and clinician specialities.

Results: Self-reported lifetime prevalences of all 30 neuropsychiatric symptoms investigated (including cognitive, sensorimotor and psychiatric) were significantly higher in SARDs than controls. Validated instruments assessed 55% of SARDs patients as currently having depression and 57% anxiety. Barriers to identifying neuropsychiatric symptoms included: (i) limits to knowledge, guidelines, objective tests and inter-speciality cooperation; (ii) subjectivity, invisibility and believability of symptoms; and (iii) under-eliciting, under-reporting and under-documenting. A lower proportion of clinicians (4%) reported never/rarely asking patients about mental health symptoms than the 74% of patients who reported never/rarely being asked in clinic ($P < 0.001$). Over 50% of SARDs patients had never/rarely reported their mental health symptoms to clinicians, a proportion underestimated at <10% by clinicians ($P < 0.001$).

Conclusion: Neuropsychiatric symptom self-reported prevalences are significantly higher in SARDs than controls, and are greatly underestimated by most clinicians. Research relying on medical records and current guidelines is unlikely to accurately reflect patients' experiences of neuropsychiatric symptoms. Improved inter-speciality communication and greater patient involvement is needed in SARD care and research.

Keywords: neuropsychiatric, mental health, systemic autoimmune rheumatic diseases, rheumatology, symptom identification, patient–clinician relationships, depression, under-reporting

Rheumatology key messages

- The range of neuropsychiatric symptoms experienced by SARD patients is wider than previously reported.
- Existing criteria are not reflective of patient experiences, contributing to widespread under-identification of neuropsychiatric symptoms.
- Greater inter-speciality and clinician–patient collaboration is required in care, research and assessment criteria design.

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Introduction

Neuropsychiatric (NP) symptoms in systemic autoimmune rheumatic disease (SARD) patients are associated with increased morbidity and mortality [1], and reduced quality of life [2]. Although multiple studies have estimated the prevalence of a range of NP symptoms, particularly depression and anxiety, in a variety of SARDs [2–4], prevalence findings vary considerably [5]. There are also gaps in the SARD literature regarding a wider range of potential NP symptoms, such as psychiatric, neuro-ophthalmological, auditory-vestibular and peripheral nervous system symptoms. Aside from SLE, where neuropsychiatric lupus (NPSLE) has been more widely researched [1, 6, 7], research on a range of NP symptoms in several SARDs is very limited, particularly UCTD and PMR [4]. Gaps in the literature are also apparent concerning the identification/non-identification of NP SARD symptoms in clinical practice, with, for example, little on the extent to which clinicians ask SARD patients about NP symptoms.

Identifying NP symptoms as SARD symptoms can assist in diagnosis and disease management [8]. However, the diverse range of potential symptoms, limited biomarkers to assist in assessing causation [9] and a lack of understanding as to aetiology [10] can inhibit identification. Attribution is complicated by SARD patient quality of life usually being substantially adversely altered [2, 11], and therefore some NP symptoms such as depression may have varying levels of a reactive component, or be multifactorial in origin [3]. Medications can also have adverse NP impacts, particularly corticosteroids [12].

In addition, it seems possible that studies have in general underestimated SARD NP symptom range and prevalence partly as the result of symptom exclusion. For example, although the SLICC group and the Italian Society of Rheumatology Study Group on NPSLE have substantially furthered understanding of NP symptoms in SLE [6, 7, 13, 14], study symptom inclusion is usually restricted to only the 19 symptoms listed in the ACR criteria [14]. Moreover, due to prevalence studies frequently relying upon what patients report to clinicians [15], eliciting/reporting biases and misattribution biases could also have an impact and may be generating an underestimation of the NP symptom burden in all SARDs. Patients may, for example, be reluctant to report NP symptoms to their clinicians for fear of being labelled with a primary psychiatric diagnosis [15, 16].

To address the identified gaps in the literature this study therefore elicited and compared patient-reported and clinician-estimated prevalences of a much broader range ($n = 30$) of potential NP symptoms than has been previously studied, and identified reasons for their under-identification by clinicians and in research.

Methods

INSPIRE project

The INSPIRE (Investigating Neuropsychiatric Symptom Prevalence and Impact in Rheumatology patient Experiences) research project consists of a series of inter-related mixed method studies exploring various aspects of SARD NP symptoms identified by patient groups and clinicians as of key importance to investigate. The quantitative and qualitative methods have been applied and integrated at every stage of the research process to complement the respective methodological strengths [17]. More details on the methodology are in Supplementary Data S1 (available at *Rheumatology* online), including symptom descriptions, recruitment and data analysis information, and the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) and COREQ (COnsolidated criteria for REporting Qualitative research) [18] checklists.

Participants and design

Preparatory work with patients and clinicians ensured the survey incorporated a broad range ($n = 30$) of NP symptoms. The final pre-tested surveys were made available between July 2022 and September 2022 (patients) or November 2022 (clinicians) internationally on the online platform Qualtrics, via social media, patient support groups and professional networks, with the following criteria specified.

Inclusion criteria for patients: 18 years and over, and reporting a SARD(s) confirmed in a clinical correspondence. Any SARD groups with $n > 50$ participants were included in the study.

Inclusion criteria for clinicians: clinicians in the following specialisms were explicitly invited to participate: rheumatology, neurology, psychiatry and primary care. Other clinicians were eligible if they had involvement with rheumatology patients' NP symptoms.

Controls were recruited by asking patient respondents to forward the control survey link to a friend with the following exclusion criteria provided: <18 years old or any serious incurable physical disease. It was made clear that having a mental health (MH) condition (however severe) did not make the person ineligible. Advantages of using 'healthy friend' controls include convenience and the increased likelihood of case–control sociodemographic similarities [19].

To reduce differing interpretations for symptoms, identical lay terminology and explanations were used for patient, control and clinician surveys. In addition to demographic information, patients and controls were asked for frequency of having experienced each symptom (in their lives) from five options: never, 1–3 times, >3 times but not often, often, always. Clinicians were asked to estimate the lifetime prevalence of NP symptoms in all SLE patients (not just their own patients). Questions on eliciting and reporting of symptoms used a 7-item Likert-type scale of increasing frequency from 0 = never to 6 = always. Validated instruments were included in the surveys to ascertain current levels of depression [PROMIS (Patient-Reported Outcomes Measurement Information System) SF8b] and anxiety [GAD-7 (Generalised Anxiety Disorder Assessment)] [20]. Interviews—with interviewees purposively selected to cover a range of sociodemographic and experience characteristics—were conducted by three experienced medical researchers and lasted from 28 min to >3 h.

Analysis

Differences between and within the groups of interest (i.e. patients, controls and clinicians) were investigated using *t*-tests, analysis of variance and Kruskal–Wallis (KW) tests, based on the distribution and the type of data. *Post hoc* tests were used where statistically significant differences were revealed. Correlations were calculated using Spearman's or Pearson's as appropriate, and χ^2 tests were used to investigate the associations between variables of interest. Adjusted logistic regression models were used to investigate the differences in outcomes between the SARDs groups. $P = 0.05$ was used

as the minimum significance. For comparing patients and controls, lifetime prevalence was defined as a participant reporting experiencing that symptom >3 times in their lives to exclude the occasional experience of common symptoms such as low mood and anxiety. SLE was selected for comparing patient self-reported NP symptoms with clinician estimates due to it being the SARD most commonly associated with NP symptoms. For this patient–clinician comparison, prevalence was defined as the patient ever having experienced a symptom.

The qualitative analysis used data from open-ended survey questions and in-depths interviews. Analysis was thematic and broadly followed Braun and Clarke's stages of analysis [21, 22]. This includes: (i) immersion in the data; (ii) developing a coding (categorization) scheme, and coding; (iii) combining participant extracts for each code; and (iv) generating themes directly from the data using the codes, and with input on interpretation from the wider study team. Addressing threats to validity included testing and developing emergent findings against additional data, triangulating qualitative and quantitative results, and discussion of conflicting views. Using a constructionist [23] qualitative paradigm also ensured the resultant themes were co-constructed between the study team and study participants.

Ethical approval

Ethical approval was obtained through the Cambridge Psychology Research Committee: PRE 2022.027. Informed consent was taken electronically at the start of the online surveys and recorded verbally on audio-recordings for interviews. The protocol and statistical analysis plan were pre-registered: https://osf.io/zrehm.

Results

This study reports on data analysed from 2605 UK and international respondent (patients = 1853, clinicians = 289, controls = 463) surveys, and interviews with 67 patients and 46 clinicians (Table 1). SARD groups included were: SLE, inflammatory arthritis, vasculitis, SS, PMR, UCTD, myositis and SSc. Participants selecting mixed/multiple SARDs on the survey were included in the combined SARD calculations. Clinician respondents (70% of whom were at consultant level) were mainly composed of rheumatologists (48%), psychiatrists (25%) and neurologists (13%). Additional participant details are in Supplementary Table S1, available at *Rheumatology* online.

Symptom prevalence

SARD patient and control self-reported NP symptoms

SARD patients had a significantly higher lifetime self-reported prevalence (experienced >3 times in their life) of all NP symptoms compared with controls (Figs 1 and 2), including after adjusting for age, gender, ethnicity and country of residence (Supplementary Table S2, available at *Rheumatology* online). Symptoms with the highest prevalence in SARDs were fatigue (mean SARD prevalence of 89% *vs* 34% in controls), insomnia (76% *vs* 49%) and cognitive dysfunction (70% *vs* 22%). PMR patients reported the lowest prevalence of NP symptoms, and SLE and UCTD patients the highest. There were significant differences in symptom frequency between males and females for 18/30 of the symptoms (11/30 were significantly more frequently experienced by females). There were weak negative correlations [maximum of r = –0.250, $P < 0.001$ (for obsessive–compulsive disorder)] between age and symptom frequency for all symptoms except for insomnia. More detailed statistics can be found in Supplementary Tables S3–S5, available at *Rheumatology* online.

Aside from in SLE where widespread NP effects were more expected, clinicians generally expressed surprise when shown the high prevalence and range of NP symptoms reported by all SARD groups. Opinions ranged from: 'they don't commonly affect the brain' [participant (Ppt) 191, Rheumatologist, England] to views that nervous system involvement was more common than currently recognized:

> *'All these autoimmune inflammatory rheumatological diseases, they all affect the brain to a greater or lesser degree… [some clinicians] are not getting this right to have as primarily a joint problem and not consider the neuropsychiatric'* (Ppt 115, Psychiatrist, USA)

Current levels of depression and anxiety

Current mean depression and anxiety scores were significantly higher for the combined SARD group than for controls (Table 2). Combined SARDs depression scores (using PROMIS SF8b) were 17.69 compared with 13.53 for controls (95% CI 3.41–4.90, $P < 0.001$). There were significant differences between SARD groups [KW = 36.97 (depression) and 69.45 (anxiety), both $P < 0.0001$; *post hoc* tests in Supplementary Table S6, available at *Rheumatology* online], with PMR patients having the lowest levels of current anxiety (37%) and depression (39%). SLE patients had the highest levels of anxiety (70%) and UCTD patients the highest levels of depression (61%). There were no significant differences in anxiety and depression scores between male and female patients.

Converting into severity of depression, 55% of SARD patients had some degree of depression (mild = 24%, moderate = 25%, severe = 6%) compared with 30% of controls overall. Some level of anxiety (using GAD-7) was found in 57% of SARDs (mild = 31%, moderate = 16%, severe = 10%) compared with 33% of controls [Table 2 (2.2 and 2.4)].

SLE patient-reported prevalence compared with clinician estimates

Clinician estimates of NP symptom prevalence were lower than SLE patient reports for all symptoms (Fig. 3A). For example, 47% of SLE patients reported having (ever) experienced suicidal thoughts compared with the median clinician estimate of 15%. The lack of consensus and range of knowledge of NP symptoms was highlighted by the large range of frequency estimates between (Fig. 3B), and within, specialities (Fig. 3C; additional figures available as Supplementary Fig. S1, available at *Rheumatology* online). Patients were unanimously unsurprised when shown the large differences between patients and clinician estimates, stating it was because clinicians did not always 'ask' or 'listen' and/or 'believe' (multiple patients). In contrast, most clinicians expressed surprise and concern. Understanding the range and prevalence of symptoms from the patients' perspective was felt to be very valuable:

> *'It is very interesting because you haven't used just the symptoms in the published criteria and this has come from the patients, so it is important for us to know. I am*

Table 1. Participant characteristics

Characteristic	Patient survey ($n = 1853$), n (%)	Patient interviews ($n = 67$), n (%)	Control survey ($n = 463$), n (%)	Clinician survey ($n = 289$), n (%)	Clinician interviews ($n = 46$), n (%)
Age (years)					
18–30	94 (5)	6 (9)	45 (10)	6 (2)	0
30–39	195 (11)	5 (7)	71 (15)	90 (31)	8 (17)
40–49	298 (16)	17 (25)	82 (18)	95 (33)	19 (41)
50–59	519 (28)	16 (24)	84 (18)	60 (21)	11 (24)
60–69 (60+ for clinicians)	478 (26)	9 (13)	120 (26)	38 (13)	8 (17)
70+	267 (14)	14 (21)	60 (13)	N/A	N/A
Prefer not to say	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Gender					
Female	1687 (91)	60 (90)	334 (72)	153 (53)	22 (48)
Male	160 (9)	7 (10)	126 (27)	131 (45)	24 (52)
Other/undisclosed	6 (<1)	0 (0)	3 (<1)	5 (2)	0 (0)
Country/region					
England	1285 (69)	38 (57)	341 (74)	126 (44)	27 (59)
Scotland	144 (8)	7 (10)	43 (9)	14 (5)	2 (4)
Wales	104 (6)	7 (10)	20 (4)	4 (1)	2 (4)
N. Ireland or Republic of Ireland	35 (2)	3 (4)	7 (2)	0 (0)	0 (0)
USA or Canada	112 (6)	4 (6)	16 (3)	47 (16)	3 (7)
Europe	121 (7)	4 (6)	24 (5)	47 (16)	5 (11)
Asia	18 (1)	1 (1)	1 (<1)	17 (6)	3 (7)
Latin America	4 (<1)	0 (0)	2 (<1)	21 (7)	3 (7)
Australia or New Zealand	19 (1)	2 (3)	0 (0)	6 (2)	0 (0)
Other	11 (<1)	1 (1)	9 (2)	7 (2)	1 (2)
Ethnicity					
White	1718 (93)	56 (84)	434 (95)		
Asian	49 (3)	7 (10)	6 (1)		
Black	23 (1)	2 (3)	4 (1)		
Mixed	40 (2)	2 (3)	11 (2)		
Other/undisclosed	23 (1)	0 (0)	2 (<1)		
Disease					
SLE	566 (31)	25 (37)			
Inflammatory arthritis	456 (25)	9 (13)			
Vasculitis	200 (11)	3 (4)			
SS	150 (8)	6 (9)			
PMR	132 (7)	7 (10)			
UCTD	77 (4)	9 (13)			
Myositis	64 (4)	3 (4)			
SSc	63 (3)	2 (3)			
Mixed/multiple	145 (8)	3 (4)			
Clinician role					
Rheumatologist				139 (48)	20 (43)
Psychiatrist				72 (25)	7 (15)
Neurologist				38 (13)	7 (15)
Rheumatology nurse				17 (6)	4 (9)
GP/primary care				11 (4)	5 (11)
Other speciality				12 (4)	3 (7)

GP: General Practitioner; N/A: Not Applicable.

worried now I have been underestimating these symptoms in my patients' (Ppt 200, Rheumatologist, Europe)

Psychiatrists' prevalence estimates were the closest to patient self-reports (Fig. 3B), and were significantly higher than neurologists' and rheumatologists' estimates (except for fatigue and cognitive dysfunction). Participants surmised this was related to psychiatrists having more time and skill to sensitively elicit NP symptoms.

Factors contributing to under-identification of NP symptoms

The qualitative analysis indicated a range of factors (combined into four themes) had contributed to under-identification of NP symptoms: Theme 1, limitations to knowledge, assessment criteria and teamwork; theme 2, subjectivity, invisibility and believability; theme 3, under-eliciting, under-reporting and under-documenting; and theme 4, describing and ascribing challenges.

Theme 1: limitations to knowledge, assessment criteria and inter-disciplinary teamwork

Clinicians frequently reported no/limited training in, and knowledge of, many of the SARD NP manifestations listed in this study, and many stated they had 'guessed' (multiple clinicians) estimates of symptom frequency. Some clinicians (and some patients) had not considered many of the surveyed NP symptoms to be potential or common manifestations of SARDs:

'*I don't think we would ask about things like their hearing because that's not often related to lupus so similarly we*

	Controls % (n=418)	Combined SARDs % (n=1813)	SLE % (n=548)	RA/IA % (n=450)	Vasculitis % (n=196)	Sjögrens % (n=149)	PMR % (n=130)	UCTD % (n=76)	SSc % (n=63)	Myositis % (n=63)	Chi Square p-values
Fatigue	34	89	94	86	89	93	81	91	87	89	<0.001
Insomnia	49	76	79	75	74	83	74	83	68	73	0.056
Cognitive dysfunction	22	70	82	66	62	77	52	78	57	57	<0.001
Weakness/loss of strength	13	63	64	57	60	60	61	70	73	84	0.002
Bowel or bladder problems	31	61	66	54	59	76	46	71	71	59	<0.001
Anxiety	41	59	68	56	58	62	39	74	49	49	<0.001
Restlessness/ agitation	32	57	67	52	57	53	42	68	44	49	<0.001
Positive sensory symptoms	20	56	63	47	63	60	40	66	49	57	<0.001
Very Low Mood	35	56	66	55	55	52	38	59	51	48	<0.001
Hypersensitivity to noise and/or light	18	55	67	44	47	65	35	72	43	41	<0.001
Palpitations	27	55	62	48	55	54	43	70	63	46	<0.001
Loss of coordination/ balance	14	51	57	49	48	55	33	58	41	65	<0.001
Dizziness/ raised HR on standing	28	50	56	44	52	54	35	62	51	46	<0.001
Disrupted dreaming sleep	31	48	57	42	47	50	38	57	37	41	<0.001
Tinnitus	28	47	47	46	43	50	44	55	48	48	0.706
Severe headache	23	46	59	40	39	46	28	62	30	30	<0.001
Disorientation	16	37	47	32	35	38	19	39	27	25	<0.001
Difficulty swallowing	9	36	39	25	29	66	14	37	71	67	<0.001
Negative sensory symptoms	8	32	38	29	31	36	18	34	32	37	0.001
Visual changes	9	31	36	27	37	34	20	34	21	30	0.002
Uncontrollable emotions	14	30	39	26	30	16	27	26	16	32	<0.001
Obsessive thoughts or compulsive behaviour	17	27	36	23	26	23	12	37	22	24	<0.001
Tremors	7	24	30	18	27	25	18	36	16	22	<0.001
Hearing loss	8	23	23	20	35	30	12	21	22	14	<0.001
Suicidal thoughts	12	19	23	16	18	17	12	25	16	21	0.043
Mania	8	16	20	13	15	11	12	12	17	14	0.011
Disinhibition	9	16	18	13	19	13	8	21	16	11	0.043
Hallucinations	4	11	15	7	12	8	4	16	17	13	<0.001
Delusions and/or paranoia	5	8	11	7	9	5	3	11	10	6	0.127
Seizures	3	5	7	4	3	7	3	8	6	2	0.091

Figure 1. Lifetime self-reported prevalence of potential neuropsychiatric symptoms in SARDs compared with controls. Percentage of controls and each disease group experiencing each symptom (>3 times in their lives) in descending order of SARDs frequency. Highest (orange) and lowest (green) prevalences are highlighted. χ^2 results are from the comparison of the individual SARD groups. Note: the combined SARDs group and chi squared comparison included the eight individual SARDs listed plus participants with mixed or multiple CTDs/SARDs. SARD: systemic autoimmune rheumatic disease

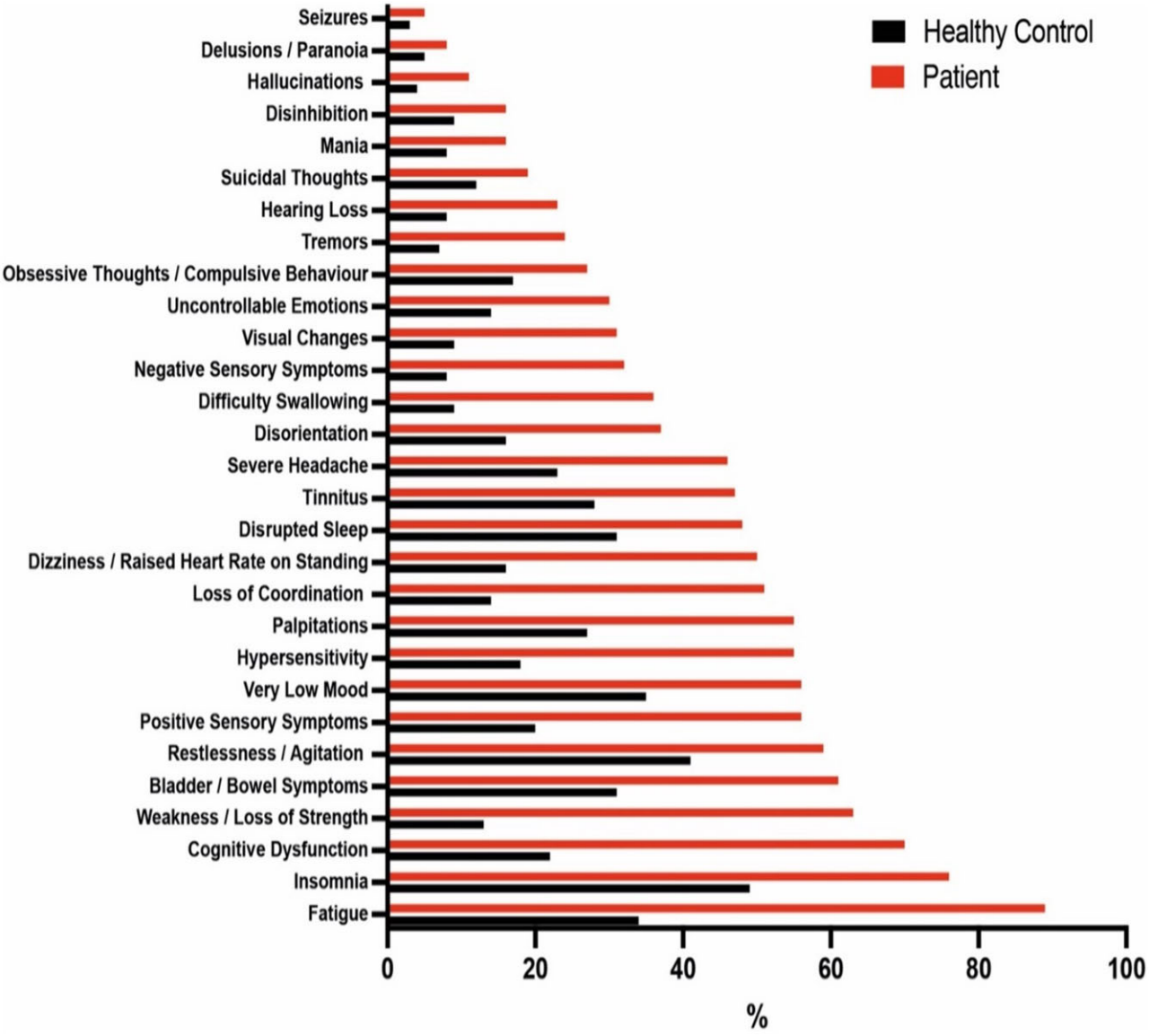


Figure 2. Comparison of self-reported lifetime (experienced >3 times in life) prevalence of individual NP symptoms between SARD patients ($n = 1813$) and healthy controls ($n = 418$). SARD: systemic autoimmune rheumatic disease

> *wouldn't ask about mood*' (Ppt 4, Rheumatologist, England)

UCTD and SS patients in particular felt that their neurological symptoms were underestimated. A common concern was that SS was assumed to be 'just dry eyes and mouth' (multiple participants). Patients from all disease groups reported diverse NP symptoms which they perceived had sometimes been overlooked clinically, resulting in adverse repercussions, including permanent damage in some cases:

> *'Nobody understands Sjögrens. My rheumatologist thinks it is a sicca disease only and refuses to even talk to me about all the neurological damage it has caused, continues to cause. I am now having to use a wheelchair as a result of advanced neuropathy'* (Ppt 257, SS, England)

Several participants raised concerns that most rheumatological disease standard assessments, such as the DAS for RA, incorporated no NP assessments, and that some clinicians may be rigidly adhering to inadequate criteria. Current models for assessing and classifying NP symptoms even in SLE were considered to be too limited:

> *'Many [SLE NP] symptoms are underestimated and not detected because they are not included in the main criteria like the ACR criteria. Something like small fibre neuropathy is very common we think but not tested often'* (Ppt 200, Rheumatologist, Europe)

Despite the acknowledged importance of multi-disciplinary teams for SARDs: 'the brain is such a complex organ it needs more than one brain working on it, more than one speciality' (Ppt 49, Psychiatrist, USA), few clinicians and patients reported hospital systems facilitating effective multidisciplinary teamwork. The psychiatrists discussed a much wider range of NP symptoms potentially affecting SARD patients—such as derealization, disinhibition, hypersensitivity

Table 2. Validated instrument scores for anxiety (GAD-7) and depression (PROMIS SF8b)

2.1 Raw GAD-7 (anxiety) scores

	Controls ($n = 409$)	Mean SARDs ($n = 1581$)	SLE ($n = 458$)	RA/IA ($n = 396$)	Vasculitis ($n = 172$)	SS ($n = 132$)	PMR ($n = 123$)	UCTD ($n = 66$)	SSc ($n = 56$)	Myositis ($n = 58$)
Raw GAD-7 scores[a] [mean (S.D.)]	3.78 (4.36)	6.50 (5.30)	7.97 (5.51)	6.16 (5.08)	5.98 (5.33)	5.68 (5.01)	4.54 (4.94)	6.5 (4.86)	5.93 (5.21)	5.81 (4.79)

2.2 GAD-7 raw scores converted into severity of anxiety: % of each group (n)

	Controls % ($n = 409$)	Mean SARDs % ($n = 1581$)	SLE % ($n = 458$)	RA/IA % ($n = 396$)	Vasculitis % ($n = 172$)	SS % ($n = 132$)	PMR % ($n = 123$)	UCTD % ($n = 66$)	SSc % ($n = 56$)	Myositis % ($n = 58$)
No anxiety	67 (273)	43 (675)	30 (136)	44 (175)	47 (81)	50 (66)	63 (78)	39 (26)	52 (29)	47 (27)
Mild anxiety	21 (87)	31 (498)	34 (155)	33 (131)	31 (54)	28 (37)	23 (28)	36 (24)	27 (15)	34 (20)
Moderate anxiety	9 (35)	16 (253)	22 (103)	15 (58)	12 (21)	14 (18)	6 (7)	17 (11)	14 (8)	14 (8)
Severe anxiety	3 (14)	10 (155)	14 (64)	8 (32)	9 (16)	8 (11)	8 (10)	8 (5)	7 (4)	5 (3)
Any degree of anxiety	33 (136)	57 (906)	70 (322)	56 (221)	52 (91)	50 (66)	37 (45)	61 (40)	48 (27)	53 (31)

2.3 Raw PROMIS SF8b (depression) scores

	Controls ($n = 412$)	Mean SARDs ($n = 1589$)	SLE ($n = 461$)	RA/IA ($n = 399$)	Vasculitis ($n = 172$)	SS ($n = 133$)	PMR ($n = 124$)	UCTD ($n = 66$)	SSc ($n = 56$)	Myositis ($n = 58$)
Raw PROMIS depression scores SF8b[b] [mean (S.D.)]	13.25 (6.51)	17.69 (8.11)	19.21 (8.76)	17.58 (7.90)	17.08 (7.78)	16.47 (7.47)	14.73 (6.82)	18.55 (8.14)	16.48 (7.82)	16.48 (7.88)

2.4 PROMIS raw scores converted into severity of depression: % of each group (n)

	Controls % ($n = 412$)	Mean SARDs % ($n = 1589$)	SLE % ($n = 461$)	RA/IA % ($n = 399$)	Vasculitis (% $n = 172$)	SS % ($n = 133$)	PMR % ($n = 124$)	UCTD % ($n = 66$)	SSc % ($n = 56$)	Myositis % ($n = 58$)
No depression	70 (290)	45 (720)	41 (188)	43 (171)	47 (81)	50 (67)	61 (76)	39 (26)	45 (25)	57 (33)
Mild depression	14 (59)	24 (372)	21 (98)	29 (114)	22 (37)	23 (30)	22 (27)	24 (16)	25 (14)	16 (9)
Moderate depression	15 (60)	25 (402)	29 (133)	22 (89)	27 (46)	24 (32)	15 (18)	30 (20)	26 (15)	24 (14)
Severe depression	1 (3)	6 (95)	9 (42)	6 (25)	5 (8)	3 (4)	2 (3)	6 (4)	4 (2)	3 (2)
Any degree of depression	30 (122)	55 (869)	59 (273)	57 (228)	53 (91)	50 (66)	39 (48)	61 (40)	55 (31)	43 (25)

[a] Min = 0, Max = 21 regardless of the group; statistically significant difference in the mean anxiety score between the control and the SARDs groups based on the t-test (95% CI), $P < 0.05$ (2.16, 3.27); Statistically significant difference in the mean anxiety score across the individual disease categories, based on Kruskal–Wallis (KW) test (KW = 69.45, $P < 0.05$). The *post hoc* tests are given in Supplementary Table S6, available at *Rheumatology* online. The significant differences were robust when adjusting for age, gender, ethnicity and country.

[b] Min = 8, Max = 40 regardless of the group; statistically significant difference in the mean depression score between the control and the SARDs groups based on the t-test (95% CI), $P < 0.05$ (3.41, 4.90); statistically significant difference in the mean depression score across the individual disease categories, based on Kruskal–Wallis test (KW = 36.97, $P < 0.05$). The *post hoc* tests are given in Supplementary Table S6, available at *Rheumatology* online. The significant differences were not robust when adjusting for age, gender, ethnicity and country. GAD: Generalised Anxiety Disorder Assessment; PROMIS: Patient-Reported Outcomes Measurement Information System; IA: inflammatory arthritis.

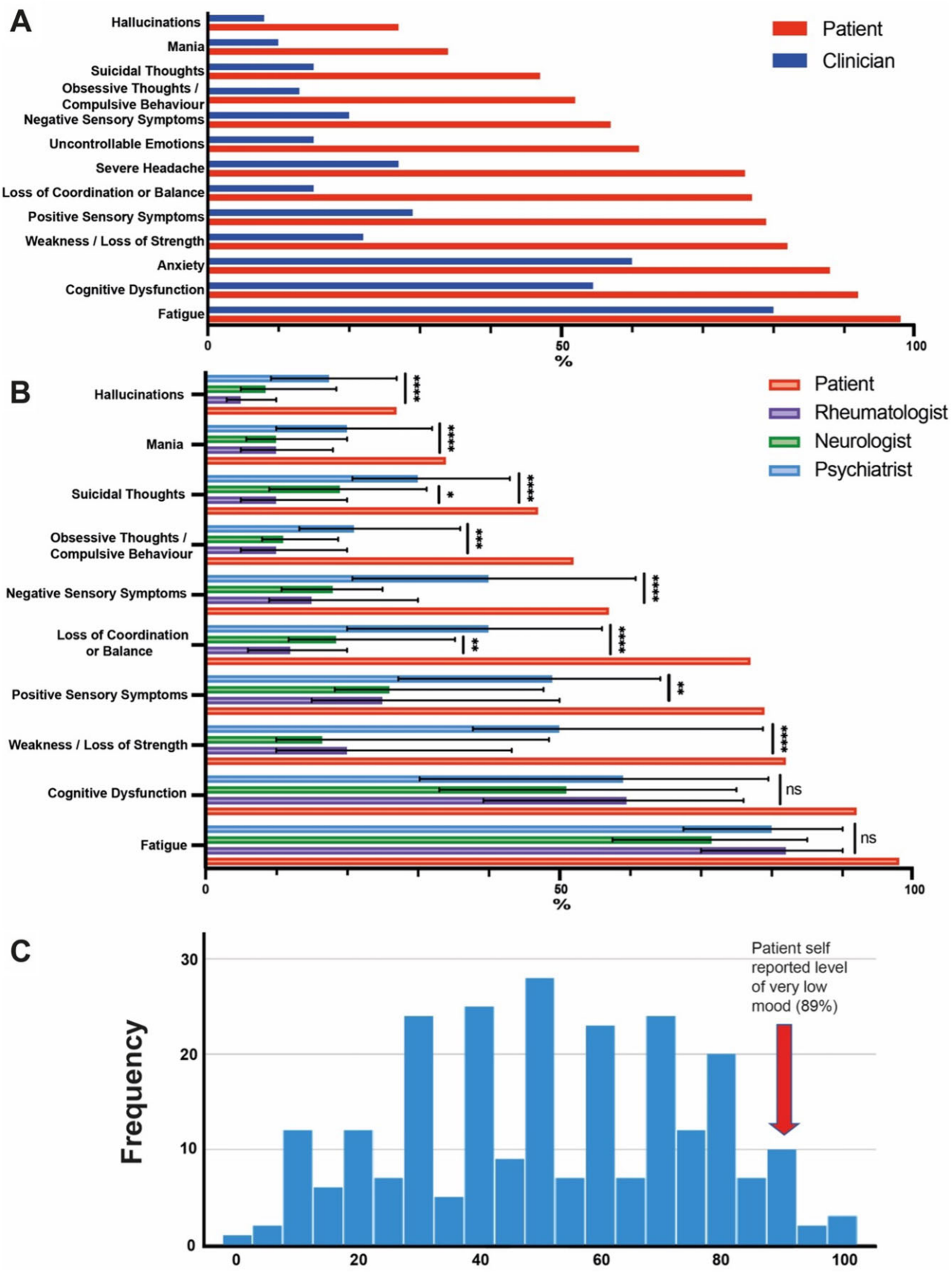


Figure 3. Lifetime (ever experienced) prevalence of NP symptoms in SLE—patient self-reports ($n = 548$) compared with clinician estimates ($n = 246$). (**A**) Patient self-reported prevalence compared with (median) clinician estimates. (**B**) Estimates of prevalence subdivided into individual specialities with IQR. (**C**) Example of large range of prevalence estimates for symptoms (using very low mood) by clinicians ($n = 246$) Further examples in Supplementary Information 2, available at *Rheumatology* online. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$; ns, not significant. NP: neuropsychiatric; IQR: interquartile range

to external stimuli—than the other specialities yet were very rarely consulted so were unable to help identify or manage these symptoms. There was strongly expressed disagreement about NP symptoms between and within specialties, and it was commonly felt that patients were often given 'contradicting messages' (Ppt 287, Psychiatrist, Latin America) and missed or misdiagnoses. Rheumatology referral systems were compared unfavourably by neurologists and psychiatrists with more established multi-disciplinary working in diseases like multiple sclerosis and HIV. Rheumatology nurses were felt to be an asset, and their holistic focus more conducive to open reporting of NP symptoms: 'We are actually much more about them rather than how are your knees, your joints, skin. . .' (Ppt 116, Rheumatology Nurse, Scotland).

Patients experiencing effective multi-disciplinary communication usually expressed a higher level of medical security:

> *'Now my rheumatologist and psychiatrist talk to each other all the time. . . without those two I don't think I'd be functioning. . . never let me down'* (Ppt 448, SLE, England)

Theme 2: subjectivity, invisibility and believability

Clinicians widely acknowledged that many SARD NP symptoms are often not detectable using existing tests, even for symptoms that were perceived to be the most directly attributable to the SARD. Serology, cerebrospinal fluid analysis, electromyographs and brain imaging were reported to more frequently be normal than abnormal even in patients with severe SARD NP manifestations: 'We find normal brain MRIs in 70% to 80% of our NPSLE patients' (Ppt 263, Rheumatologist, Asia)

However, access to and knowledge of tests (such as for cytokines, IFNs or complement activation products) considered to be potentially more enlightening in detecting neuroinflammation was reported to be very limited outside of research. Most clinicians therefore principally used tests to exclude infections and other non-SARD causes for NP symptoms. Only a minority of clinicians specified that tests must be abnormal for an NP symptom to be identified and to: 'count' [it depended on] 'looking for that objective evidence' (Ppt 76, Neurologist, England), and 'localising symptoms. . . that's what we do as neurologists' (Ppt 162, neurologist, England). Most clinicians felt that 'diffuse' (multiple clinicians) NP symptoms were more common in systemic autoimmunity:

> *'These complex diseases, they often don't have clearly objective, localised symptoms so you need to look deeper and understand the connection between the central and the peripheral nervous systems, the immune system, and the gastrointestinal systems, the cardiovascular system. These patients often have interactions between all of these and that's what underlies that lack of localisation for these symptoms'* (Ppt 67, Neurologist, USA)

Limited availability and accuracy of objective testing and the invisibility of many NP symptoms contributed to many patients feeling disbelieved:

> *'The rheumatologists that I have dealt with, actually only treat visible symptoms. That the symptoms that they can't see cannot be trusted to be the truth given by the patient'* (Ppt 83, SS, Wales)

Many patients and clinicians highlighted the importance of listening to and believing patient reports: 'Your first thought is not I'll do a blood test to check if they're telling the truth. . . you just sort of believe them' (Ppt 57, Psychiatrist, England). Relying solely on subjective reports was complicated by some clinicians feeling that patients did not always understand or accurately report their NP symptoms. However, other clinicians felt that patients had more insight into these symptoms than they were sometimes given credit for:

> *'People who have these chronic diseases they really know their own body. . . patients know themselves and listening is most important and valuing their views will often be more enlightening, and if we don't listen then it's usually because we are afraid that we don't know enough'* (Ppt 79, Psychiatrist, England)

There were multiple reports that clinicians interpreted patient reports of diverse symptoms without corresponding objective evidence as psychogenic, further reducing the chance of identifying and documenting these multiple symptoms and also reducing patients' future willingness to report.

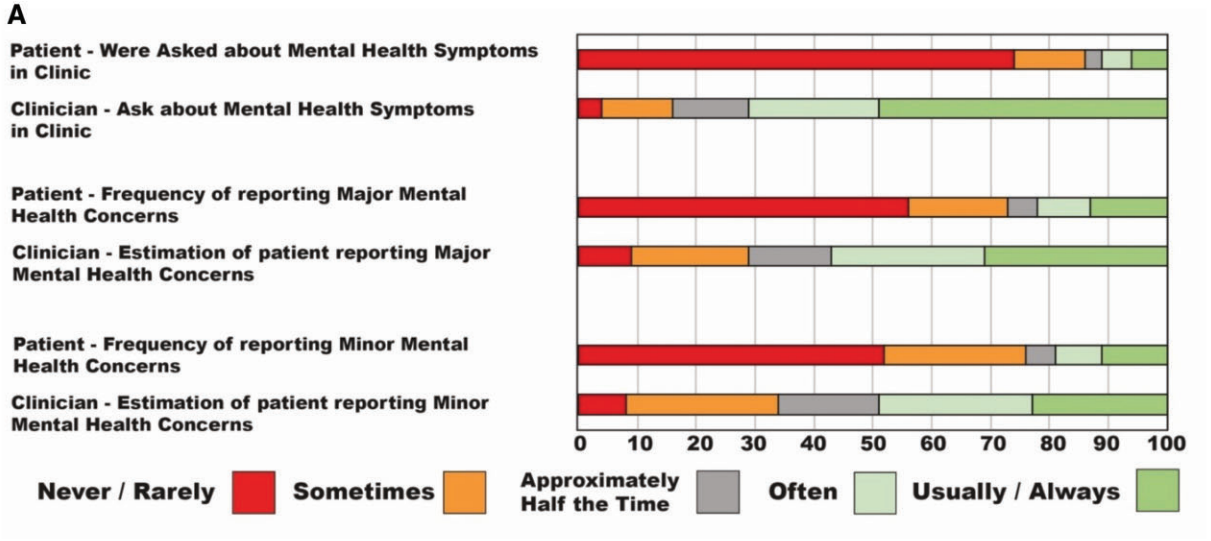
Theme 3: under-eliciting, under-reporting and under-documenting of NP symptoms

A significantly lower proportion of clinicians reported never/rarely asking rheumatology patients about MH symptoms compared with patients who reported they had never/rarely been asked about MH in clinic (4% *vs* 74%, $P < 0.001$) (Fig. 4A). This difference was discussed in interviews with some participants surmising that clinicians may have counted a general 'how are you?' as having asked the patient about their MH, whereas patients were expecting more specific questions as a follow-up to their—often polite and non-informative—initial response: 'No one asks probing questions', 'I'm fine' type answers aren't questioned' (Ppt 260, England, inflammatory arthritis). Moderate positive correlations were found between frequencies of being explicitly asked about MH and reporting MH symptoms ($r = 0.38$ for major MH and $r = 0.42$ for minor MH, both $P < 0.001$).

Over 50% of patients had never/rarely reported their MH symptoms to a clinician. Patient reporting frequencies were significantly different from clinician perceptions where clinician mean frequency estimate was 3.67 (on a scale of 0 = never to 6 = always) of reporting major MH symptoms compared with the patient mean of 1.79 (95% CI –2.14, –1.62, $P < 0.001$) (Fig. 4A). Patients from the USA were significantly more likely than those from mainland UK to report MH symptoms to a clinician, and to report being asked about their MH by clinicians (Supplementary Information 2, available at *Rheumatology* online).

Several clinicians stated that they did not ask about symptoms such as hallucinations and delusions because they would be unmissable, or they did not know how to approach the topic. Other clinicians and most patients identified extreme reticence and stigma associated with reporting such symptoms, and the importance of asking explicitly: 'doctors don't go looking for it [hallucinations] so if we don't ask we don't think it exists much' (Ppt 14, Rheumatology Nurse, England).

A



Category***	Mean (± SD) patient frequencies N=1803*	Mean (± SD) clinician estimates N=287	Mean Difference	95% Confidence Interval	P Value**
Asked about MH symptoms in clinic	1.08 (± 1.54)	4.23 (± 1.86)	-3.14	-3.34, -2.95	<0.001
Reporting of major MH concerns	1.79 (± 1.89)	3.67 (± 2.04)	-1.88	-2.14, -1.62	<0.001
Reporting of minor MH concerns	1.80 (± 1.75)	3.66 (± 2.16)	-1.86	-2.09, -1.62	<0.001

B

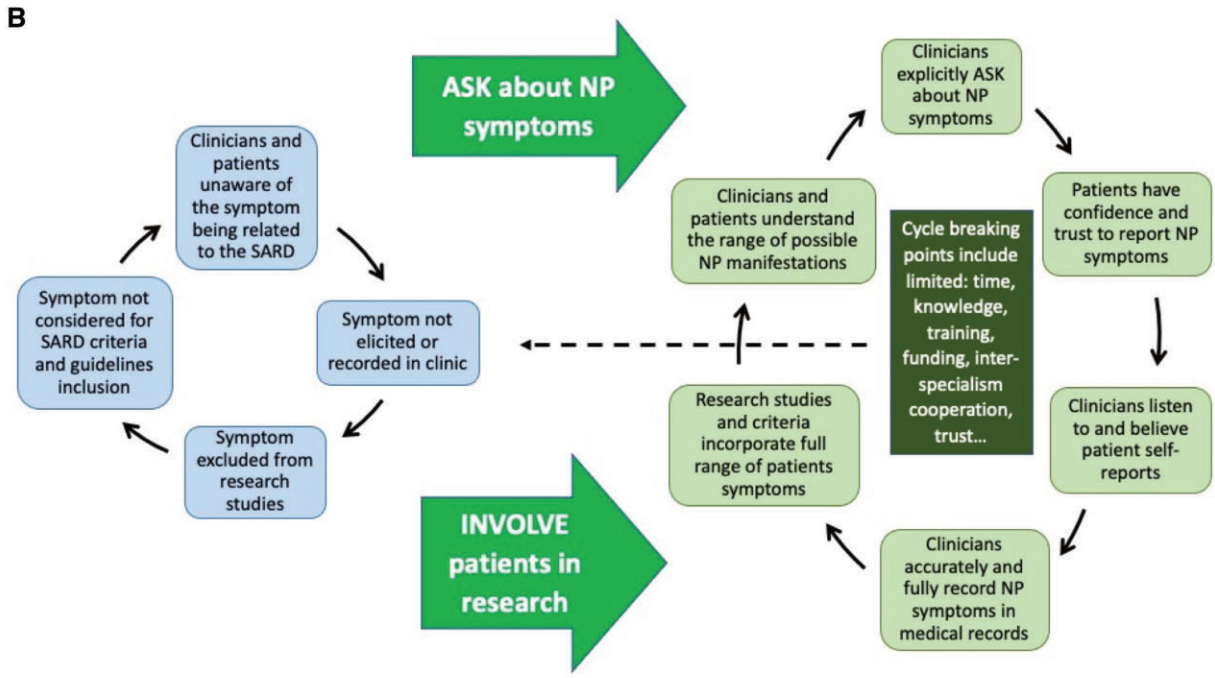


Figure 4. Under-identification of neuropsychiatric symptoms in care and research. (**A**) Frequencies of eliciting and reporting MH symptoms in clinician practice. SARD patients ($n = 1803$) and clinicians ($n = 287$). *At most, due to some patients not having MH concerns to report. **Paired *t*-test. ***0 = never to 6 = always. (**B**) Model of movement between the cycles of NP symptom identification/non-identification. SARD: systemic autoimmune rheumatic disease; MH: mental health; NP: neuropsychiatric

Aside from time constraints, the most frequently cited reasoning for non-disclosure was a fear of future disease symptoms being misattributed to MH, or a common experience of past disease symptoms being disbelieved or misattributed to psychological/psychogenic causes:

> *'During the start of my vasculitis I was told it was all in my mind and that I needed to think positively… I buried my feelings after that'* (Ppt 423, Vasculitis, England)

Patients also frequently reported that even when they did share their NP symptoms, they were often not commented on and/or not documented accurately or at all. SARD clinic letters and medical records were felt often to be 'too brief' (Ppt 7, General Practitioner, England) and to under-report the quantity and severity of symptoms reported: 'letters my rheumatologist writes that don't cover even half of what we talked about… ignores all my neurological symptoms' (Ppt 52, UCTD, England). General Practitioners and other specialists relied on information from rheumatologists, and also felt the focus was rarely on NP symptoms.

The under-documenting, under-eliciting and under-reporting appears to have contributed to a self-perpetuating cycle with researchers, clinicians and patients then being unaware of the possible NP symptoms to be covered in research, criteria and clinic (Fig. 4B).

Theme 4: describing and ascribing challenges

Patients and clinicians discussed—and indeed demonstrated in interviews—difficulties in describing NP symptoms, arising from the absence of a clear and shared terminology:

> *'The way patients understand and use these words and the way we [clinicians] use these words can be a major limitation… [even] neurologists, rheumatologists and psychiatrists don't agree on the terminology and even if we do it's all very vague'* (Ppt 162, Neurologist, England)

Although the survey requested that symptom prevalence estimates not be influenced by opinions of the degree of attribution directly to the SARD, clinicians surmised that attribution considerations may have reduced identification in clinic and prevalence estimates by some clinicians: 'including in their [prevalence] assessments of whether it's 'organic'' (Ppt 76, Neurologist, England).

Regardless of the disparate views of attribution, the vast number of survey and interview responses describing decimated lives highlights the urgency of improving identification, and therefore support, for these often life-changing symptoms:

> *'Feel guilty and useless as well as depressed and very unwell. I don't really feel supported, understood, listened to, hopeful at all. It is awful living like this… all just feels hopeless'* (Ppt 926, SLE, England)

Discussion

This mixed methods, international study found that the self-reported lifetime prevalence of NP symptoms in multiple SARD patient groups was significantly higher than in the physically healthy controls, and underestimated by most clinicians. Symptom identification was hindered by patients and clinicians often not being aware of the wide range of possible NP symptoms to raise these in clinic appointments, by clinicians not explicitly asking, and by patients being reluctant to report their NP symptoms. In addition, when patients did attempt to report their NP symptoms, some perceived that their reports were not always listened to, believed, discussed in detail or documented. Our finding that >50% of SARDs patients never/rarely reported their NP symptoms to clinicians not only highlights the importance of clinicians explicitly asking about these symptoms in clinic, but also indicates the value of research obtaining symptom and other data directly from the patients. While self-reported prevalence rates are subject to other potential biases such as recall bias [24], research that relies solely on often inaccurate or incomplete [25] medical records and clinician assessments [1, 6] may be underestimating NP symptom range and prevalence.

While SARD NP prevalence estimates vary greatly between studies [5], the overall level and range of NP symptoms we identified was higher than indicated in the literature. Our patient data conflicted with research reporting nervous system involvement as being 'quite unusual' [26] in RA, 'rare but not negligible' in SS [27] and suggesting that the 'central nervous system is one of the very few organs that is not involved' in SSc [28]. Hallucinations and psychosis are rarely considered to be related to SARDs other than SLE aside from occasional case reports [29, 30], yet our data show significantly higher self-reported prevalences of hallucinations than in controls in multiple other SARDs including SSc, vasculitis and UCTD. There is very limited research into UCTD NP manifestations, yet self-reported prevalences were highest in the UCTD group for 16 out of 30 NP symptoms included in our study. Most clinicians felt their ability to identify NP symptoms was hindered by limited time, and the lack of specific biomarkers and diagnostic tests [5], and often normal investigations [31] in SARD NP disease. Identifying SARD NP symptoms therefore remains largely reliant on patient reports and clinician judgement [6, 31]. This is a concern given the identified under-reporting, and clinicians' extremely varied prevalence estimates and candour about their own, and other specialties', limitations in identifying SARDs NP symptoms. Identifying many NP SARD symptoms in clinic and research is therefore highly reliant on listening to, and believing, a patient's subjective reports [15]. This research highlights the importance of greater use of patient-reported outcomes measures for subjective symptoms which can only be evaluated by the patient [32], such as headache and fatigue. Interviews indicated that psychiatrists' prevalence estimates being the closest to patient self-reports may reflect the ability to empathetically elicit and value subjective reports, although this may also have been influenced by longer appointments, and the majority of referrals to psychiatrists being for patients with the most severe symptoms. Psychiatrists could be a particularly valuable addition to more SARD patients' care, and in identifying the NP symptoms that are not currently (and some may never be) detectable using objective tests. In contrast, some clinicians prioritizing objective test results and localizable symptoms may be hindering identification of the diffuse NP symptoms reported as more common in SARDs [1].

We suggest that there has been a self-perpetuating cycle, in which NP symptoms are under-elicited in clinic, under-identified in research and excluded from trial outcomes [33], and have limited [14, 34] or non-inclusion in SARD criteria/

guidelines [35]. Our data and clinician participants strongly endorse the calls to update the ACR NPSLE criteria [36, 37], which remains widely used despite being reported as having low reliability and 'quite unsatisfactory' performance in clinical practice [6]. In addition, guideline development and care for other SARDs should give more consideration to NP symptoms. This may be facilitated by the greater 'multi-disciplinary international collaborative research' [36] suggested to help meet NP SARD research goals, yet few of our clinician participants worldwide reported effective systems for inter-disciplinary clinical and academic collaboration between rheumatology, neurology and psychiatry. Our research has also demonstrated the importance of fully including the patients as equal collaborators [38–40], in line with EULAR guidance [41], and to ensure 'change and innovation' [40]. Greater appreciation of this unique, yet currently under-utilized, patient knowledge [42] may reduce the underestimations of NP manifestations we identified and the frequency of diagnostic errors [15, 42], and ensure assessment criteria are more reflective of patients' actual experiences. Furthermore, although classification criteria were intended for selecting reasonably homogeneous patients for research purposes, many clinicians felt some colleagues were (and some demonstrated in interviews) misunderstanding and misusing them inflexibly in diagnosis, symptom identification and management.

This study also identified optimism for the future. Almost all clinicians were highly motivated to improve SARD NP care. Interviews and recent research demonstrates rapidly evolving NP knowledge including the behavioural and cognitive impacts of chronic inflammation [43] and a widening range of potential biomarkers [44], including serum IFN [45], cerebrospinal fluid interleukins [46] and complement activation products [47]. Strengths of our study included that we endeavoured to incorporate the symptoms experienced by the patients, and of importance to them, by asking multiple SARD patient groups to list and discuss their NP symptoms prior to survey design. Our study psychiatrists also suggested that symptoms affecting other patient groups with autoimmune brain conditions [48], such as hypersensitivity and disinhibition, may be unrecognized SARD NP symptoms. We therefore included a much broader range of symptoms than has been previously researched rather than being constrained by previous SARD criteria. An additional strength of our research is the multi-disciplinary research team which includes patients as equally valued contributors, and ensures what is 'important to patients' [38] is prioritized.

This study was designed to encourage further exploration, discussion and inclusion of a greater range of SARD NP symptoms in research and clinic, rather than as an epidemiological survey to accurately assess prevalence. The methods used therefore had multiple limitations regarding generalizability including that responses were subject to recall bias [24], diagnoses were self-stated, and survey recruitment was via social media and professional networks. The self-selecting nature of online surveys may exclude the most unwell and the most disadvantaged, and may attract those with stronger opinions in both patient and clinician groups. Our survey also recruited a lower proportion of male patients and those from minority ethnic groups than is representative of the SARD population, as is common in rheumatological research [49, 50]. In addition, controls may not have been representative of the general population, although common symptoms such as anxiety were similar to previously reported general population prevalences [20]. Clinician participants being largely recruited through Twitter and professional networks may not be socio-demographically representative of the whole clinician population, and those choosing to complete surveys to be of patient benefit may be those with a more patient-centred focus. For example, the extreme difference between patients feeling they rarely/never asked about MH (>70%) and clinician respondents having much lower values of never/rarely asking (<5%) may be partially due to the clinicians who were least interested in asking patients about MH also being the least likely to respond to a survey about MH symptoms. There was also no facility for ascertaining whether the symptom was NP. For example, difficulty swallowing will be a neurological symptom in some, but in other patients it may be as a result of fibrosis (e.g. in SSc) or lack of saliva production (e.g. in SS). Furthermore, although clinicians and patients were provided with identical lay descriptions of symptoms, in-depth interviews revealed that they had differing interpretations for some symptoms. This included in differentiating weakness from fatigue, and potentially in different use of terminology, such as symptoms or syndromes. While our symptom list was more diverse and strived to be more reflective of the patient experiences than previous research, it was by no means exhaustive. Further limitations are included in Supplementary Data S1, available at *Rheumatology* online.

Conclusions

This study provides substantial evidence that the NP symptom burden is higher and more wide-ranging in the majority of SARDs than has previously been recognized, and that symptoms are often under-reported and under-recorded. More effective inter-disciplinary and patient–clinician collaboration is required to identify symptoms, and to design criteria and research that is more reflective of the SARD NP symptoms experienced by patients.

The next stages of the INSPIRE project will investigate: attribution of NP symptoms, eliciting and reporting of NP symptoms, the impact of these symptoms on patient lives, and specific challenges and inequalities experienced by SARD patients from ethnic minorities.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Anonymized data will be available on reasonable request following the completion of the INSPIRE studies.

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